IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
Group Art Unit 1624

In re

Patent Application of

David Edwin Thurston, et al.

Serial No. 10/021,213

Filed: December 12, 2001

Confirmation No. 1106

Examiner: Unknown

"PYRROLOBENZODIAZEPINES"

I, Leslie Rector, hereby certify that this correspondence is being deposited with the US Postal Service as first class mail in an envelope addressed to Commissioner for Patents, Washington, D C 20231, on the date of my signature.

Leslie Rector
Signature

September 11, 2002
Date of Signature

SECOND PRELIMINARY AMENDMENT

Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants submit herewith a second preliminary amendment prior to examination of this application on the merits and respectfully requests entry of the following amendments.

In the Specification:

Please amend the specification as follows:

On page 1, please delete the title "PYRROLBENZODIAZEPINES", and replace it with the following:

PYRROLOBENZODIAZEPINES

Replace the paragraph found on page 13, lines 28-35 and continuing on page 14, lines 1-7 with the following:

Aspects of the invention will now be further described with reference to the accompanying drawings in which:

Figures 1 to 6a/b are synthesis routes for compounds of formula **Ia** of the present invention;

Figures 7 to 14 are synthesis routes for compounds of formula **II** of the present invention;

Figures 15 to 24 are synthesis routes for compounds of formula **III** of the present invention;

Figure 25 is a synthesis route for a compound of formula **IV**;

Figure 26 is a synthesis of an intermediate in the preparation of compounds of formula **IV** of the present invention;

Figure 27 is a synthesis routes for compounds of formula **IV** of the present invention; and

Figures 28 to 31 are graphs illustrating the cytotoxicity results of examples 5 to 8 respectively.

Replace the title paragraph found on page 152, lines 14-16 with the following:

Example 3(g) : 8-Hydroxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (130, DRH-168)

Replace the title paragraph found on page 157, lines 22-23 with the following:

Examples 3(h) to (j) : Synthesis of 7-Phenyl PBDs (See Figure 21)

Replace the title paragraph found on page 164, lines 14-16 with the following:

Example 3(k) : 8-Benzyloxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (143, DRH-105) (see Figure 22)

Replace the title paragraph found on page 166, lines 15-16 with the following:

Example 3(l) : Synthesis of the C8-NH_2 PBD (151, AG/149) (see Figure 23)

Replace the title paragraph found on page 171, lines 4-6 with the following:

Example 3(m) : Synthesis of (11aS)-8-methyl-7,9-dimethoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (194) (see Figure 24)

Replace the title paragraph found on page 175, lines 11-15 with the following:

Example 4 : Synthesis of the C8-Amines

Synthesis of 3-(11-Hydroxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxy-2-propenylpropanoate (159) (see Figure 26)

Replace the title paragraph found on page 181, lines 1-3 with the following:

Example 4(a) :3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-perhydro-1-pyrrolyl-1-propanone (161)(see Figure 27)

Replace the title paragraph found on page 183, lines 14-16 with the following:

Example 4(b) : 3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-piperidino-1-propanone (163) (see Figure 27)

Replace the title paragraph found on page 185, lines 3-5 with the following:

Example 4(c) : 1,(2,3-dihydro-1*H*-indolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-propanone (165) (see Figure 27)

Replace the title paragraph found on page 187, lines 1-3 with the following:

Example 4(d) : 1,(2,3-dihydro-1*H*-2-isoindolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-propanone (167) (see Figure 27)

Replace the title paragraph found on page 189, lines 1-4 with the following:

Example 4(e) : Synthesis of (11aS) 8-(N-9-fluorenylmethoxycarbonyl)aminopropyloxy-7-methoxy-1,2,3,11a-tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (205) (See Figure 25)

Replace the paragraph found on page 200, lines 28-31 with the following:

Example 5 : *In Vitro* Cytotoxicity of compounds of formula I

Some of the compounds synthesised in example 1, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC_{50};μM) are set out below, and are illustrated in Figure 28.

Replace the paragraph found on page 202, lines 1-4 with the following:

Example 6(a) : *In Vitro* Cytotoxicity of compounds of Formula II

Some of the compounds synthesised in example 2, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC_{50};μM) are set out below, and are illustrated in Figure 29.

Replace the paragraph found on page 206, lines 1-4 with the following:

Example 7 : *In Vitro* Cytotoxicity of compounds of Formula III

All of the compounds synthesised in example 3, were subjected to the NCI *In Vitro* Cytotoxicity screen. The results (LC_{50};μM)are set out below, and are illustrated in Figure 30.

Replace the paragraph found on page 207, lines 6-9 with the following:

Example 8 : *In Vitro* cytotoxicity of compounds of Formula IV:

The compounds synthesised in example 4, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC_{50};μM) are set out below, and are illustrated in Figure 31.

In the Drawings:

Please cancel duplicate Figure 24, page 26/32.

Enclosed are copies of the drawing Figures 1-31 (31 sheets) showing the proposed changes in red ink.

Remarks:

Consideration of the foregoing amendments and following remarks is respectfully requested.

The title has been amended to correct a typographical error.

The remaining amendments to the specification cancel all references to omitted drawing Figure 21, relabel the drawing figures to be numbered consecutively, and correct the references in the specification to the drawing figures to correspond with any relabeled drawing figures. Omission of FIG. 21 was noted per a "Notice of Omitted Item(s) in a Nonprovisional Application" mailed 02/19/02 (copy attached). As was indicated in the 02/19/02 "Notice of Omitted Item(s) in a Nonprovisional Application," this paper is being submitted prior the first office action. It occurs to the undersigned that a substitute specification (including all of the above deletions) might make this application easier to examine. The undersigned is willing to provide such a substitute specification should it be requested.

For reasons provided above, Applicants respectfully submit that the amendments to the specification introduced herein adds no new matter to the application.

Conclusion:

With the entry of the foregoing amendments, Applicants respectfully submit that all claims are in condition for allowance and request favorable action thereon.

Respectfully submitted,

Grady J. Frenchick 9/11/02

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"Version with markings to show changes made"

The changes made to the specification are shown by [brackets] for deleted matter, and double underlining for added matter.

In the specification, page 1.

[PYRROLBENZODIAZEPINES] PYRROLOBENZODIAZEPINES

In the specification, page 13, lines 28-35 and continuing on page 14, lines 1-7.

Aspects of the invention will now be further described with reference to the accompanying drawings in which:
Figures 1 to 6a/b are synthesis routes for compounds of formula **Ia** of the present invention;
Figures 7 to 14 are synthesis routes for compounds of formula **II** of the present invention;
Figures 15 to 2[5]4 are synthesis routes for compounds of formula **III** of the present invention;
Figure 2[6]5 is a synthesis route for a compound of formula **IV**;
Figure 2[7]6 is a synthesis of an intermediate in the preparation of compounds of formula **IV** of the present invention;
Figure 2[8]7 is a synthesis routes for compounds of formula **IV** of the present invention; and
Figures 2[9]8 to 3[2]1 are graphs illustrating the cytotoxicity results of examples 5 to 8 respectively.

In the specification, page 152, lines 14-16.

Example 3(g) : 8-Hydroxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (130, DRH-168) [(see Figure 21)]

Replace the title paragraph found on page 157, lines 22-23 with the following:

Examples 3(h) to (j) : Synthesis of 7-Phenyl PBDs (See Figure 2[2]1)

Replace the title paragraph found on page 164, lines 14-16 with the following:

Example 3(k) : 8-Benzyloxy-7,9-dimethoxy-1,2,3,11a-tetrahydropyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (143, DRH-105) (see Figure 2[3]2)

Replace the title paragraph found on page 166, lines 15-16 with the following:

Example 3(l) : Synthesis of the C8-NH_2 PBD (151, AG/149) (see Figure 2[4]3)

Replace the title paragraph found on page 171, lines 4-6 with the following:

Example 3(m) : Synthesis of (11aS)-8-methyl-7,9-dimethoxy-1,2,3,11a-tetrahydro-5H-pyrrolo[2,1-c][1,4]benzodiazepin-5-one (194) (see Figure 2[5]4)

Replace the title paragraph found on page 175, lines 11-15 with the following:

Example 4 : Synthesis of the C8-Amines

Synthesis of 3-(11-Hydroxy-5-oxo-10-(2,2,2-trichloroethyloxocarbonylamino)-(11aS)-2,3,5,10,11,11a-hexahydro-1*H*-

benzo[*e*]pyrrolo[2,1-*a*][1,4]diazepin-8-yloxy-2-propenylpropanoate (159) (see Figure 2[7]6)

Replace the title paragraph found on page 181, lines 1-3 with the following:

Example 4(a) :3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-perhydro-1-pyrrolyl-1-propanone (161)(see Figure 2[8]7)

Replace the title paragraph found on page 183, lines 14-16 with the following:

Example 4(b) : 3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-piperidino-1-propanone (163) (see Figure 2[8]7)

Replace the title paragraph found on page 185, lines 3-5 with the following:

Example 4(c) : 1,(2,3-dihydro-1*H*-indolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-propanone (165) (see Figure 2[8]7)

Replace the title paragraph found on page 187, lines 1-3 with the following:

Example 4(d) : 1,(2,3-dihydro-1*H*-2-isoindolyl)-3-(7-methoxy-5-oxy(11aS)-2,3,5,11a-tetrahydro-1*H*-benzo[*e*]pyrrolo[1,2-*a*][1,4]diazepin-8-yloxy)-1-propanone (167) (see Figure 2[8]7)

Replace the title paragraph found on page 189, lines 1-4 with the following:

Example 4(e) : Synthesis of (11aS) 8-(N-9-fluorenylmethoxycarbonyl)aminopropyloxy-7-methoxy-1,2,3,11a-

tetrahydro-5*H*-pyrrolo[2,1-*c*][1,4]benzodiazepin-5-one (205) (See Figure 2[6]5)

Replace the paragraph found on page 200, lines 28-31 with the following:

Example 5 : *In Vitro* Cytotoxicity of compounds of formula I

Some of the compounds synthesised in example 1, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC_{50};μM) are set out below, and are illustrated in Figure 2[9]8.

Replace the paragraph found on page 202, lines 1-4 with the following:

Example 6(a) : *In Vitro* Cytotoxicity of compounds of Formula II

Some of the compounds synthesised in example 2, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC_{50};μM) are set out below, and are illustrated in Figure [30]29.

Replace the paragraph found on page 206, lines 1-4 with the following:

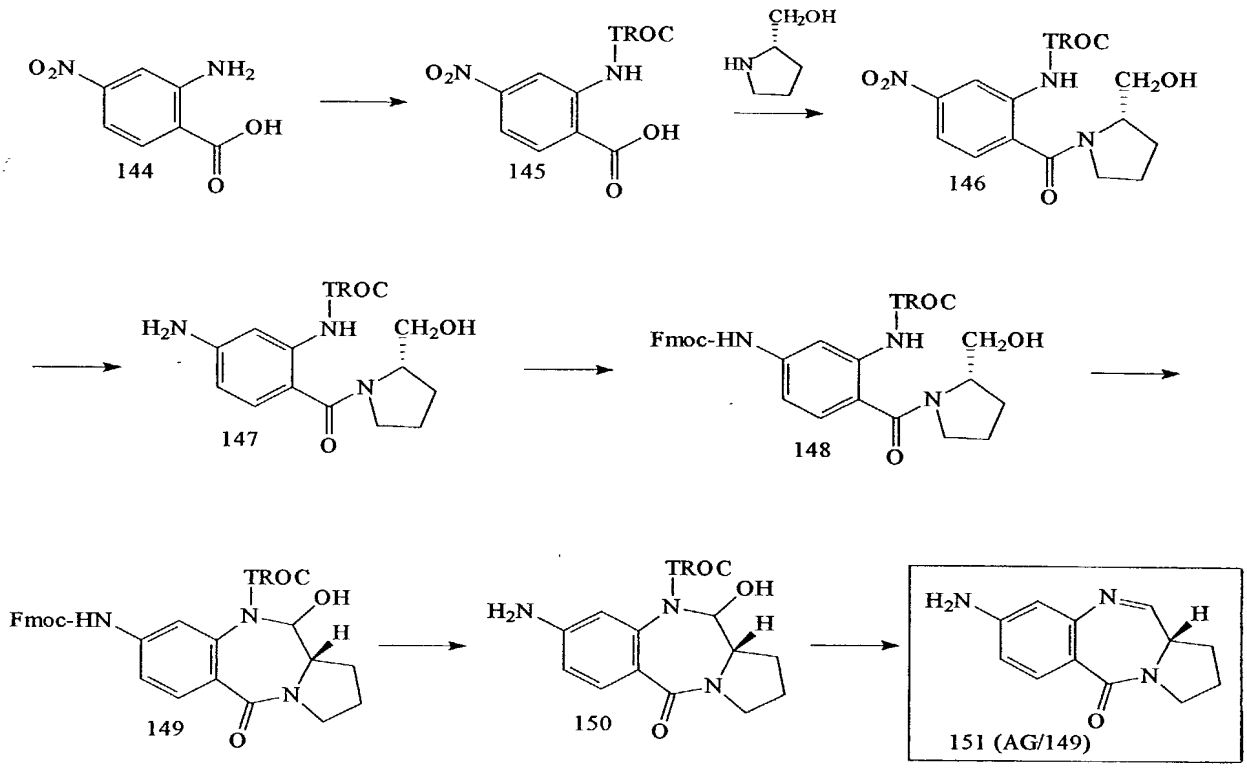
Example 7 : *In Vitro* Cytotoxicity of compounds of Formula III

All of the compounds synthesised in example 3, were subjected to the NCI *In Vitro* Cytotoxicity screen. The results (LC_{50};μM)are set out below, and are illustrated in Figure 3[1]0.

Replace the paragraph found on page 207, lines 6-9 with the following:

Example 8 : *In Vitro* cytotoxicity of compounds of Formula IV:

The compounds synthesised in example 4, were subjected to the NCI *In Vitro* Cytotoxicity study. The results (LC_{50};μM) are set out below, and are illustrated in Figure 3[2]1.



cancel

~~Figure 24~~